2 SYNOPSIS

Name of Sponsor:	Dr. Kade Pharmazeutische Fabrik GmbH Rigistraße 2 D-12277 Berlin Germany	
Name of finished Product:	Posterisan® akut mit Lidocain 60 mg/ Zäpfchen	
Name of Active Substance(s):	Lidocaine	

Title:	Placebo-controlled double-blind trial investigating the efficacy and tolerability of Posterisan® akut mit Lidocain 60 mg/ Zäpfchen in abatement of complaints associated with haemorrhoids.
Investigators:	XXX, Schönhauser Allee 43, D-10453 Berlin, Germany A listing of all investigators is provided in Appendix 16.1.4.
Study centre(s):	10 study centers in Germany.
Publication (reference)	None as of date of report.
Studied period: (date of first enrolment) (date of last completed)	Clinical Phase: 07-JAN-2013 27-AUG-2013 III
Objectives:	To prove superior efficacy of Posterisan® akut mit Lidocain 60 mg/ Zäpfchen in the relief of symptoms related to haemorrhoids compared with placebo (suppositories).
Study design:	Prospective, multicenter, randomized, placebo-controlled, double-blind study with 2 parallel treatment arms. Generally, eligible study patients were screened and randomized at Day 0 (Baseline). The patients treated themselves at home for 3 days (Days 1-3) and completed a patient diary for daily symptom assessment. They returned to the study site for a final assessment on Day 4 (accepted time window of +3 days).
Study population:	Adult males or females with complaints related to haemorrhoids (pain, burning or itching).
Diagnosis and criteria for inclusion:	• Legally valid informed consent for study participation. • Age ≥18 years. • Patients with symptoms related to haemorrhoids (pain, burning or itching) • At least one of the symptoms of haemorrhoids (ie,

	pain or burning or itching) must have an intensity of ≥65 as measured on a visual analog scale (VAS). Important exclusion criteria in terms of medical history included the presence of intra- or perianal thromboses, Grade III-IV haemorrhoids, fissures, Type IV hypersensitivity, confirmed rectal carcinoma, anorectal infections, and chronic inflammatory bowel disease.
Test product, dose, batch number:	Posterisan® akut mit Lidocain 60 mg/ Zäpfchen. The suppositories were to be inserted into the rectum 2-3 times per day (single dose: 60 mg lidocaine) for a total treatment duration of 3 days. Used batch number was: K071252
Reference therapy, dose, batch number:	Suppository base with no active substance. The mode of application was identical as for the verum suppository. Used batch number was: K071251
Duration of treatment:	3 days (Days 1-3).
Criteria of evaluation:	
Efficacy	Note: All symptoms of haemorrhoids (pain, burning, itching) were assessed by patients using a 100 mmVAS. <u>Primary efficacy endpoint:</u> • Change (improvement) from Baseline (Day 0) in the most bothersome symptom (MBS; defined as the most annoying haemorrhoidal symptom at Baseline) at the day of treatment completion (Day 3). <u>Secondary efficacy endpoints:</u> • Change (improvement) from Baseline in MBS at treatment Days 1 and 2. • Between-group comparison of MBS responder rates (response defined as an absolute value ≤30 mmVAS) at the day of treatment completion (Day 3). The preceding analyses of MBS changes were repeated separated by type of MBS (ie, by pain, burning or itching, subgroup analyses). <u>Further endpoints:</u> • Mean changes in each haemorrhoidal symptom from Baseline (Day 0) to final study assessment (Day 4).
Safety	Occurrence of local and systemic adverse events during the study period. In addition, the tolerability was assessed by patients and investigators on a 5-point ordinal scale.

Statistical methods:	Descriptive analyses: Generally, all continuous data were displayed with mean, standard deviation, extreme values, median, and 25%- and 75%- quantiles. Categorical data were described with tabulated summaries including absolute and relative frequencies. Primary efficacy analysis: The primary analysis was performed with the ITT population and applying the LOCF approach for missing values. The primary endpoint (change in MBS from Baseline [Day 0] at Day 3) was compared between treatment groups in a confirmatory fashion using the non-parametric Mann-Whitney U test (2-sided α=0.05). In addition to the precise p-value derived from this test, the effect size estimator "MWE" based on the Mann-Whitney U statistics (U/n x m; probability of concordance, with MWE=0.5 indicating maximum overlap, and the theoretical ranges of 0 and 1 indicating no overlap) with its 95% confidence intervals was provided, as well as the non-parametric Hodges Lehmann estimate (HLE) for the between-group difference in the VAS changes with its corresponding 95%-CIs. Additional sensitivity analyses to support the results of the primary efficacy analysis comprised the use of the PP population and different methods of data imputation (observed cases analysis, worst case scenario, best case scenario) in the ITT population. Secondary efficacy analyses: Changes from Baseline in MBS at treatment Days 1 and 2 were analyzed similar to the primary analysis at Day 3. The MBS responder rates were compared between treatment groups with Fisher's exact test and the Odds Ratio (OR) calculated as effect size measure. Subgroup analyses included the repetition of the pooled MBS analyses separated by type of MBS (ie, burning, itching, pain). These analyses were performed in the same way as for the main MBS analyses. Further efficacy analysis: Changes in the single anorectal symptoms from Baseline at Day 4 were analyzed descriptively, but not statistically compared between treatment groups. Safety analyses: Adverse events were coded using the MedDRA terminology and summarized in frequency tables by treatment group and in total. Where applicable, Fisher's exact test was used to compare incidence rates between groups. Ordinal tolerability assessments by investigators and patients were summarized descriptively in frequency tables.

Efficacy Results:

Patient disposition:

A total of 203 patients enrolled at 10 sites entered the study, 203 received study medication and were valid for the safety and ITT analyses (102 in the Posterisan akut group and 101 in the placebo group), while 173 patients (85 Posterisan akut, 88 placebo) were valid for the PP analyses.

Demographic and other baseline characteristics:

The 203 study patients (52.2% females, 47.8% males) had a mean age of 53.1 $\pm$ 14.9 years (range: 19-90 years). The most frequently reported MBS at Baseline was "itching" (62.6% of patients), followed by "burning" (21.2%) and "pain" (16.3%). Overall, there were no relevant treatment group differences at Baseline in terms of the demographic and other baseline characteristics, including symptom intensity and the distribution of the MBS.

Primary efficacy results:

The course of the MBS in the ITT population (LOCF), the change from Baseline at Day 3 and the tests for the difference in changes between treatment groups (treatment contrast) are summarized in Table A. Based on the Hodges Lehmann estimate, the numerical difference in the median changes was 6.5 mmVAS in favor of Posterisan akut, and the MWE of 0.511 indicated an at least small effect in favor of Posterisan akut. However, the confirmatory statistical test (p-value from Mann-Whitney U test) and, descriptively, the 95%-CIs for the effect sizes measures (HLE and MWE) failed to show that the observed difference is statistically significant. All sensitivity analyses yielded similar results.

Table A: Primary efficacy analysis: Changes in the MBS from Baseline (Day 0) at Day 3 (ITT, LOCF)

	Posterisan akut N=102	Placebo N=101
Day 0 (mmVAS)		
mean ± STD	77.6 ± 9.6	78.9 ± 9.6
median (min:max)	75.0 (50.0:100.0)	78.0 (65.0:100.0)
Q1 / Q3	70.0 / 83.0	70.0 / 85.0
Day 3 (mmVAS)		
mean ± STD	44.3 ± 23.9	46.0 ± 25.0
median (min:max)	45.0 (0.0:94.0)	48.0 (0.0:96.0)
Q1 / Q3	29.0 / 64.0	26.0 / 66.0
Difference (Day 0 minus Day 3)		
mean ± STD	33.3 ± 24.1	32.9 ± 25.7
median (min:max)	32.5 (-9.0:94.0)	26.0 (-20.0:100.0)
Q1 / Q3	15.0 / 49.0	15.0 / 53.0
Test statistics for difference		
p-value*	0.788	
Mann-Whitney estimator [95%-CI]†	0.511 [0.431; 0.591]	
Hodges Lehmann estimate [95%-CI]‡	1.0 [-6.0; 8.0]	

CI=Confidence interval, max=maximum, min=minimum, Q=quartile, STD=Standard deviation
*: Mann-Whitney U test.
†: Probability of concordance (calculated as U/n x m), with values >0.5 indicating a higher probability for a better outcome on Posterisan akut compared to placebo.
‡: Non-parametric estimator for the treatment contrast; ie, the difference (Posterisan akut minus placebo) in the changes from Baseline (mmVAS); asymptotic estimate for CI.

Secondary efficacy results:

Responder rates: In this secondary analysis of the MBS, the results of the primary efficacy analysis were confirmed to the effect that the response rates were similar in both treatment groups (30.4 % in Posterisan akut group and 27.7 % in placebo group, p-value for Fisher's exact test equals 0.758).

Changes in MBS at Days 1 and 2: Mean changes in MBS from Baseline at Days 1 and 2 in the ITT population (LOCF) were numerically similar in both treatment groups (Day 1: mean change 17.8±23.8 mmVAS in the Posterisan akut group and 16.8±19.3 mmVAS in the placebo group, Day 2: 25.0±22.1 in the Posterisan akut group and 25.4±21.8 in the placebo group, p-value 0.790).

Subgroup analyses:

"Pain" was relatively infrequent reported as MBS (Posterisan akut: 14 patients, placebo group: 19 patients). The mean change from Baseline at Day 3 in the ITT population (LOCF) was 28.6±16.9 mmVAS (median: 27.5 mmVAS) in the Posterisan akut group and 34.8±28.8 mmVAS (median: 30.0 mmVAS) in the placebo group. The corresponding contrast based on the Hodges Lehmann estimate was 5.0 mmVAS with a p-value of 0.597.

For "burning" (Posterisan akut: 24 patients, placebo group: 19 patients) no remarkable group differences were observed. The mean change from Baseline at Day 3 in the ITT population (LOCF) was 37.4 ± 24.9 mmVAS (median: 39.5 mmVAS) in the Posterisan akut group and 26.7 ± 21.7 mmVAS (median: 20.0 mmVAS) in the placebo group; the

corresponding contrast based on the Hodges Lehmann estimate was 15.0 mmVAS. This distinct treatment contrast resulted in a p-value of 0.250.

For the prevailing MBS "itching" (64 patients in the Posterisan akut group and 63 patients in the placebo group), the improvement from Baseline to Day 3 was similar in both treatment groups (mean change by 32.8 ± 25.1 vs. 34.2 ± 25.9 mmVAS) with a p-value of 0.826.

Safety Results:

As expected due to the short observation period, the incidence of adverse events in either treatment group was rather low and similar among treatment groups (10.8% vs. 10.9% patients; p=1.000). Almost all of the reported AEs 21 in Posterisan akut arm/17 in placebo arm) were considered drug-related (17/12 events in 11/11 patients with AEs). One serious adverse event was reported in the placebo group.

The most frequently reported adverse event on preferred term level in either treatment group was "abdominal distension" (4) and “diarrhea” (3) in the Posterisan akut group and “anorectal discomfort” (3) and “diarrhea” (3) in the placebo group.

Generally, almost all of the reported adverse events in either treatment group (9 versus 9) belonged to the SOC "gastrointestinal disorders" and seemed to be associated with manifestations of the study disease, or local hypersensitivity reactions to the study treatment.

The remaining adverse events belonged to the SOCs “General disorders and administration site conditions” (2 versus 0), Infections and infestations (0 versus 1), Nervous system disorders (3 versus 2) and Skin and subcutaneous tissue disorders (1 versus 1).

Four patients (3 on Posterisan akut and 1 on placebo) had at least one severe adverse event reported.

Overall, event outcomes judged as "unresolved" were reported in 1 patient of the Posterisan akut group (“eczema” + “anal fissure”) and 4 patients of the placebo group (“eczema”; anorectal discomfort”; “anal abscess”; “anorectal discomfort”).

Local/global tolerability of the study treatment was mainly assessed by subjects and investigators to be "very good" or "good" at the end of the treatment period. Assessments of patients and investigators were almost congruent.

Overall, the AE pattern was quite similar in the 2 treatment groups, and there was no robust indication that treatment with Posterisan akut might be associated with a special risk of certain AEs compared to placebo. Thus, study treatment showed to be safe and well tolerated, and no new or unexpected safety signals were observed.

Conclusion

The formal primary efficacy endpoint (superiority in MBS improvement at Day 3) was not met, since the observed group difference did not become statistically significant.

Considerable improvements from Baseline at Day 3 in the MBS were observed in either treatment group but the corresponding statistical confirmatory test failed to show a statistically significant difference for these improvements. Similar results were found in the corresponding sensitivity analyses using observed cases, best or worst case scenarios, or the PP population for analyses Thus, the efficacy results observed in this study indicated that Posterisan akut does not provide an intrinsic therapeutic benefit that goes beyond the application of a plain suppository base.

However, the study data indicate that Posterisan akut is a safe and well tolerated medicinal product.

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